PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 7/06, 7/07

A1

(11) International Publication Number: **WO 95/24885**

(43) International Publication Date: 21 September 1995 (21.09.95)

(21) International Application Number: PCT/US95/02902

(22) International Filing Date: 10 March 1995 (10.03.95)

(30) Priority Data:
213,954 16 March 1994 (16.03.94) US

(60) Parent Application or Grant
(63) Related by Continuation
US 213,954 (CON)
Filed on 16 March 1994 (16.03.94)

(71) Applicant *(for all designated States except US)*: HANDELMAN, Joseph, H. [US/US]; 26 West 61st Street, New York, NY 10023 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: AHLUWALIA, Gurpreet, S. [US/US]; 8632 Stable View Court, Gaithersburg, MD 20879 (US). SHANDER, Douglas [US/US]; 16112 Howard Landing Drive, Gaithersburg, MD 20878 (US).

(74) Agents: RICHARDS, John et al.; Ladas & Parry, 26 West 61st Street, New York, NY 10023 (US).

(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TT, UA, UG, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: INHIBITION OF HAIR GROWTH

(57) Abstract

Mammalian hair growth is reduced by applying to the skin an inhibitor of a cysteine synthetic pathway enzyme.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	**GB**	United Kingdom	**MR**	Mauritania
AU	Australia	**GE**	Georgia	**MW**	Malawi
BB	Barbados	**GN**	Guinea	**NE**	Niger
BE	Belgium	**GR**	Greece	**NL**	Netherlands
BF	Burkina Faso	**HU**	Hungary	**NO**	Norway
BG	Bulgaria	**IE**	Ireland	**NZ**	New Zealand
BJ	Benin	**IT**	Italy	**PL**	Poland
BR	Brazil	**JP**	Japan	**PT**	Portugal
BY	Belarus	**KE**	Kenya	**RO**	Romania
CA	Canada	**KG**	Kyrgystan	**RU**	Russian Federation
CF	Central African Republic	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CG	Congo			**SE**	Sweden
CH	Switzerland	**KR**	Republic of Korea	**SI**	Slovenia
CI	Côte d'Ivoire	**KZ**	Kazakhstan	**SK**	Slovakia
CM	Cameroon	**LI**	Liechtenstein	**SN**	Senegal
CN	China	**LK**	Sri Lanka	**TD**	Chad
CS	Czechoslovakia	**LU**	Luxembourg	**TG**	Togo
CZ	Czech Republic	**LV**	Latvia	**TJ**	Tajikistan
DE	Germany	**MC**	Monaco	**TT**	Trinidad and Tobago
DK	Denmark	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**US**	United States of America
FI	Finland	**ML**	Mali	**UZ**	Uzbekistan
FR	France	**MN**	Mongolia	**VN**	Viet Nam
GA	Gabon				

INHIBITION OF HAIR GROWTH

The invention relates to a method for the inhibition of unwanted hair growth in mammals.

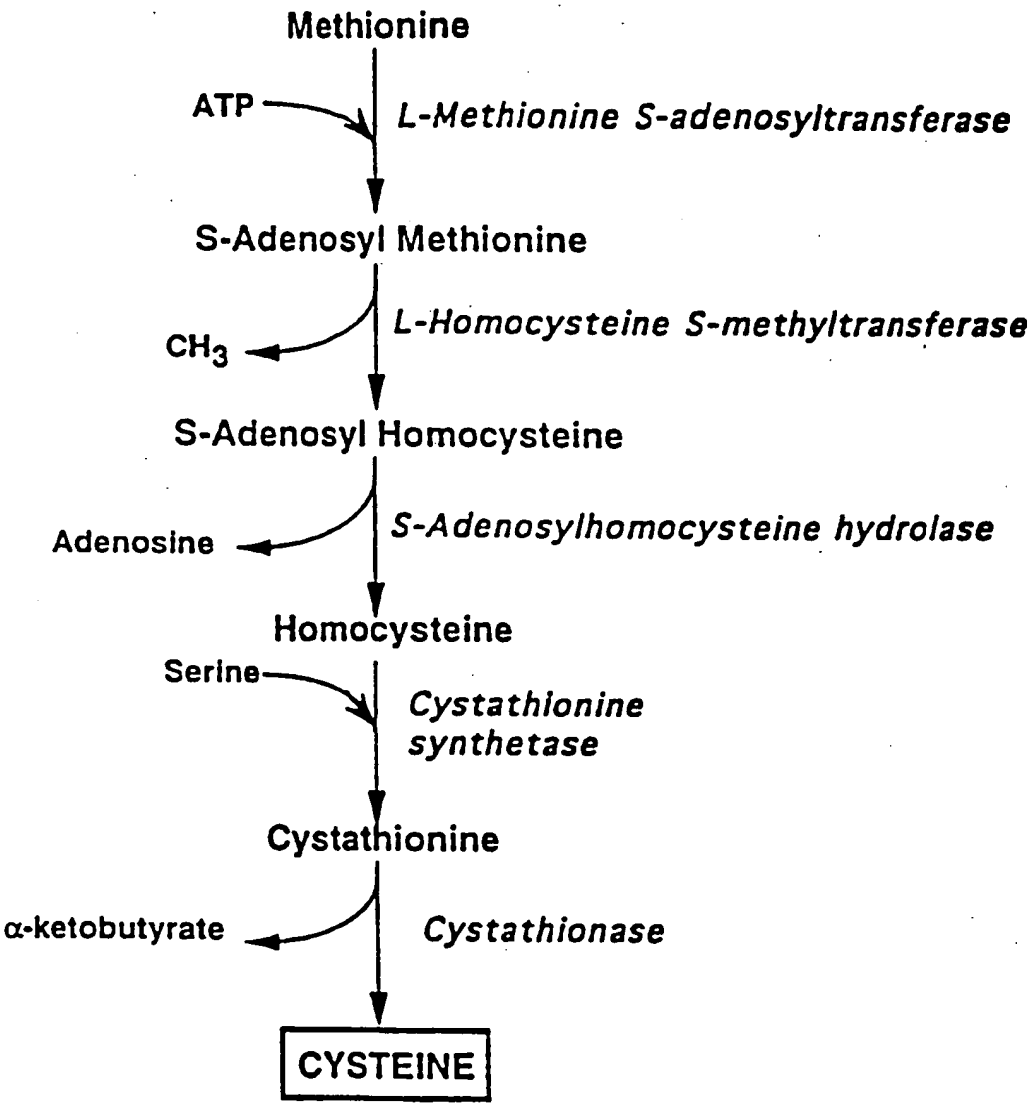
A main function of mammalian hair is to provide environmental protection. However, that function has largely been lost in humans, in whom hair is kept or removed from various parts of the body essentially for cosmetic reasons. For example, it is generally preferred to have hair on the scalp but not on the face.

Various procedures have been employed to remove unwanted hair, including shaving, electrolysis, depilatory creams or lotions, waxing, plucking, and other cosmetic procedures, and therapeutic antiandrogens. These conventional procedures generally have drawbacks associated with them. Shaving, for instance, can cause nicks and cuts, and can leave a perception of an increase in the rate of hair regrowth. Shaving also can leave an undesirable stubble. Electrolysis, on the other hand, can keep a treated area free of hair for prolonged periods of time, but can be expensive, painful, and sometimes leaves scarring. Depilatory creams, though very effective, typically are not recommended for frequent use due to their high

irritancy potential. Waxing and plucking can cause pain, discomfort, and poor removal of short hair. Finally, antiandrogens -- which have been used to treat female hirsutism -- can have unwanted side effects.

It has previously been disclosed that the rate and character of hair growth can be altered by applying to the skin inhibitors of certain enzymes. These inhibitors include inhibitors of 5-alpha reductase, ornithine decarboxylase, S-adenosylmethionine decarboxylase, gamma-glutamyl transpeptidase, and transglutaminase. See, for example, Breuer et al., U.S. Pat. No. 4,885,289; Shander, U.S. Pat. No. 4,720,489; Ahluwalia, U.S. Pat. No. 5,095,007; Ahluwalia et al., U.S. Pat. No. 5,096,911; Shander et al., U.S. Pat. No. 5,132,293; and Shander et al., U.S. Pat. No. 5,143,925.

Cysteine is synthesized in cells from methionine according to the following biochemical pathway:


Methionine
ATP
L-Methionine S-adenosyltransferase
S-Adenosyl Methionine
CH3
L-Homocysteine S-methyltransferase
S-Adenosyl Homocysteine
Adenosine
S-Adenosylhomocysteine hydrolase
Homocysteine
Serine
Cystathionine synthetase
Cystathionine
α-ketobutyrate
Cystathionase
CYSTEINE

In the initial step in the pathway, L-methionine S-adenosyltransferase converts L-methionine to S-adenosyl methionine by transferring the adenosyl moiety of ATP to L-methionine. In the second step, L-homocysteine S-methyltransferase converts the S-adenosyl methionine to S-adenosyl-L-homocysteine by transferring the methyl group of S-adenosyl methionine to an acceptor molecule present in the cell. Next, S-adenosyl homocysteine hydrolase (adenosylhomocysteinase) converts the S-adenosyl-L-homocysteine to L-homocysteine, releasing adenosine in the process. Then, cystathionine synthase catalyzes the condensation of the L-homocysteine with L-serine to form L-cystathionine. Finally, cystathionase (cystathionine gamma-lyase) hydrolyzes the L-cystathionine to form L-cysteine.

The enzymes in the biochemical pathway described above will be referred to herein as the "cysteine synthetic pathway enzymes." It has now been found that unwanted mammalian (including human) hair growth -- particularly androgen-stimulated hair growth -- can be inhibited by applying to the skin a composition including an inhibitor of a cysteine synthetic pathway enzyme in an amount effective to reduce hair growth. The unwanted hair growth which is reduced may be normal hair growth, which is cosmetically reduced, or hair growth that results from an abnormal or diseased condition.

Among the inhibitors that can be used are inhibitors of L-methionine S-adenosyltransferase such as cycloleucine, selomethionine, L-2-amino-4-methoxy-cis-but-3-enoic acid, and 2-aminobicyclo [2.1.1]hexane-2-carboxylic acid; inhibitors of S-adenosyl

homocysteine hydrolase such as 3-deazaneplanocin, adenosine-5'-carboxaldehyde, 3-deazaadenosine, and S-3-deazaadenosyl-L-homocysteine; inhibitors of cystathionine synthase such as isonicotinicacid hydrazide, O-succinyl serine, adenosine, and 6-azauridine-2',3',5'-triacetate; and inhibitors of cystathionase such as D,L-2-amino-4-pentynoic acid (D,L-propargylglycine), β,β-dichloro-D,L-alanine, β,β,β-trifluoroalanine, and L-aminoethoxyvinylglycine. All of these compounds are known and most are commercially available. Irreversible inhibitors are preferred; reversible inhibitors (competitive and non-competitive) can also be used.

The inhibitors of a cysteine synthetic pathway enzyme preferably are incorporated in a topical composition or cosmetic composition which preferably includes a non-toxic dermatologically acceptable vehicle or carrier which is adapted to be spread upon the skin. Examples of suitable vehicles are acetone, alcohols, or a cream, lotion, or gel which can effectively deliver the active compound. One such vehicle is disclosed in co-pending application PCT/US93/05068. In addition, a penetration enhancer may be added to the vehicle to further enhance the effectiveness of the formulation.

The concentration of the inhibitor in the composition may be varied over a wide range up to a saturated solution, preferably from 0.1% to 30% by weight or even more; the reduction of hair growth increases as the amount of inhibitor applied increases per unit area of skin. The maximum amount effectively applied is limited only by the rate at which the inhibitor

penetrates the skin. Generally, the effective amounts range from 100 to 3000 micrograms or more per square centimeter of skin.

The composition should be topically applied to a selected area of the body from which it is desired to inhibit hair growth. For example, the composition can be applied to the face, particularly to the beard area of the face, i.e., the cheek, neck, upper lip, and chin. The composition can also be applied to the legs, arms, torso or armpits. The composition is particularly suitable for inhibiting the growth of unwanted hair in women suffering from hirsutism or other conditions. In humans, the composition should be applied once or twice a day, or even more frequently, for at least three months to achieve a perceived reduction in hair growth. Reduction in hair growth is demonstrated when the frequency of hair removal is reduced, or the subject perceives less hair on the treated site, or quantitatively, when the weight of hair removed by shaving (i.e., hair mass) is reduced.

Male intact Golden Syrian hamsters are considered acceptable models for human beard hair growth in that they display oval shaped flank organs, one on each side, each about 8 mm. in major diameter, which grow thick black and coarse hair similar to human beard hair. These organs produce hair in response to androgens in the hamster. To evaluate the effectiveness of a composition including an inhibitor, the flank organs of each of a group of hamsters are depilated by applying a thioglycolate based chemical depilatory (Surgex). To one organ of each animal 25 μl. of vehicle alone once a day is applied, while to the other organ of each

animal an equal amount of vehicle containing an inhibitor of a cysteine synthetic pathway enzyme is applied. After thirteen applications (one application per day for five days a week), the flank organs are shaved and the amount of recovered hair (hair mass) from each is weighed. Percent-reduction of hair growth is calculated by subtracting the hair mass (mg) value of the test compound treated side from the hair mass value of the vehicle treated side; the delta value obtained is then divided by the hair mass value of the vehicle treated side, and the resultant number is multiplied by 100.

The above-described assay will be referred to herein as the "Golden Syrian hamster" assay. Preferred compositions provide an inhibition in hair growth of at least about 32%, more preferably at least about 50%, and most preferably at least about 70% when tested in the Golden Syrian hamster assay. A number of inhibitors of cysteine synthetic pathway enzymes were tested in the Golden Syrian hamster assay; the results are provided in Table 1.

TABLE 1

Inhibitor	Dose	Vehicle	pH	Hair Mass: Treated (mg mean ± SEM)	Hair Mass: Control (mg mean ± SEM)	Percent Inhibition (mean ± SEM)
3-Deazaneplanocin	5%	A	4.5	0.357±0.15	2.363±0.35	86.65±4.81
6-Azauridine-2',3',5'-triacetate	20%	A	7.0	0.455±0.05	2.372±0.14	80.25±2.37
O-Succinyl serine	15%	A	8.0	0.710±0.07	2.043±0.18	63.58±4.69
Adenosine	10%	A	4.5	1.140±0.12	2.619±0.24	55.28±4.00
Isonicotinic acid hydrazide	20%	A	8.5	1.344±0.18	2.139±0.22	35.13±7.98
DL-Propargylglycine	15%	B	9.5	1.401±0.14	2.148±0.19	33.12±5.59
3,3,3,-Trifluoro-DL-alanine	20%	A	7.5	1.110±0.13	1.681±0.13	32.36±8.01
Isonicotinic acid hydrazide + DL-Propargylglycine	10%+ 10%	B	9.0	0.920±0.29	2.385±0.74	60.72±4.69

Vehicle A: Pure water (68%), ethanol (16%), propylene glycol (5%), dipropylene glycol (5%), benzyl alcohol (4%), and propylene carbonate (2%)

Vehicle B: Pure water (73%), propylene glycol (20%), benzyl alcohol (5%), and N-methyl-2-pyrrolidone (2%)

Topical application of compositions including 3-deazaneplanocin demonstrate that an increased dosage level of the inhibitor provided an increased inhibition in hair growth. The results are provided in Table 2.

TABLE 2

	Dose	Vehicle	pH	Hair Mass: Treated (mg)	Hair Mass: Control (mg)	Percent Inhibition (mean ± SEM)
3-Deazaneplanocin	0.25%	A	4.5	1.889±0.15	2.213±0.08	86.65±4.81
3-Deazaneplanocin	0.50%	A	5.0	1.487±0.16	2.366±0.26	35.49±4.62
3-Deazaneplanocin	1.00%	A	5.0	1.113±0.08	2.303±0.11	50.94±4.77
3-Deazaneplanocin	5.00%	A	5.0	0.357±0.15	2.363±0.35	86.65±4.81

Hair follicles were isolated from the flank organs which were treated with either an inhibitor of a cysteine pathway enzyme or the carrier without the inhibitor (the control). L-Cystathionine, homocysteine, and S-adenosyl homocysteine, which are involved in a pathway leading to cysteine synthesis, were measured by an amino acid analysis method. The amino analysis of hamster flank organ hair follicles was carried out using a commercially available system (Pico-Tag; Waters Associates, Inc., Milford, MA). Hair follicle amino acids were extracted with 0.1N HCL, a derivatized with phenylisothiocyanate to yield the phenylthiohydantion derivatives of the respective amino acids, which were then separated by C-18 reverse phase chromatography and quantitated by in-line UV spectrophotometry.

More specifically, 250-500 μl of 0.1 N HCL was added to each flank organ hair follicle sample, followed by treatment with a sonicator device to obtain cell extracts. The cell extracts were centrifuged at 12,000 x g for 5 min, and the recovered supernatant was filtered through 0.45 μ filter. The filtrate was vacuum dried under nitrogen using the Pico-Tag work station. Samples were then derivatized with phenylisothiocyanate reagent by the procedure described in the Waters Associates Pico-Tag manual. An aliquot of the derivatized sample was injected on a C-18 reverse phase column (Pico-Tag column) and the elution was carried out with a gradient buffer system. This procedure separated the amino acids L-cystathionine, homocysteine, and S-adenosyl homocysteine from other amino acids present in hair follicle extracts. The amino acid

concentrations were determined at UV wavelength 254 nm using an in-line spectrophotometer and a dedicated HPLC control and data analysis system (Waters Associates). The results are provided in Table 3.

TABLE 3

	Dose	Vehicle	pH	Percent of Untreated Control (100%) L-Cystathionine	Homocysteine	S-Adenosyl Homocysteine
Vehicle control	--	A	4.5	100	100	100
3-Deazaneplanocin	0.125%	A	4.5	49	--	144
3-Deazaneplanocin	0.250%	A	4.5	29	--	149
3-Deazaneplanocin	0.500%	A	5.0	12	--	218
6-Azauridine-2',3',5'triacetate	20%	A	7.0	60	--	--
O-Succinyl serine	15%	A	8.0	66	228	--

It will be appreciated by those skilled in the art that the invention can be performed within a wide range of equivalent parameters of composition and conditions without departing from the spirit or scope of the invention or of any embodiment thereof.

C L A I M S

1. A method of inhibiting mammalian hair growth which comprises

selecting an area of skin from which reduced hair growth is desired; and

applying to said area of skin an inhibitor of a cysteine pathway enzyme in an amount effective to reduce hair growth.

2. The method of claim 1, wherein said inhibitor is cycloleucine, selenomethionine, L-2-amino-4-methoxy-cis-but-3-enoic acid, 2-aminobicyclo[2.1.1]hexane-2-carboxylic acid, 3-deazaneplanocin, adenosine-5'-carboxaldehyde, 3-deazaadenosine, S-3-deazaadenosyl-L-homocysteine, isonicotinicacid hydrazide, O-succinyl-serine, 6-azauridine-2',3',5'-triacetate, adenosine, D,L-2-amino-4-pentynoic acid, β,β-dichloro-D,L-alanine, β,β,β-trifluoroalanine or L-aminoethoxyvinylglycine.

3. The method of claim 1, wherein said inhibitor is an inhibitor of L-methione S-adenosyltransferase, an inhibitor of L-homocysteine S-methyltransferase, an inhibitor of S-adenosyl homocysteine hydrolase, an inhibitor of cystathionine synthase or an inhibitor of cystathionase.

4. The method of claim 1, wherein said inhibitor is an irreversible inhibitor.

5. The process of claim 1, wherein said inhibitor is applied as part of a composition including a dermatologically acceptable vehicle.

6. The method of claim 5, wherein the concentration of said inhibitor in said composition is between 1% and 30%.

7. The method of claim 5, wherein the composition provides a reduction in hair growth of at least 30%, preferably at least 50%, more

preferably at least 70%, when tested in the Golden Syrian hamster assay.

8. The method of claim 1, wherein the inhibitor is applied to the skin in an amount of from 100 to 3000 micrograms of said inhibitor per square centimeter of skin.

9. The method of claim 1, wherein said mammal is a human.

10. The method of claim 4, wherein said area of skin is on the face of a human.

11. The method of claim 9, wherein said area of skin is on a leg, an arm, an armpit or the torso of the human.

12. The method of claim 1, wherein said inhibitor is an irreversible inhibitor of a cysteine synthetic pathway enzyme.

13. The method of claim 1, wherein said inhibitor is a reversible inhibitor of a cysteine synthetic pathway enzyme.

14. A method according to any one of claims 1 to 13, wherein said applying of said inhibitor has a cosmetic effect.

15. A method of producing a composition for inhibiting mammalian hair growth, which comprises selecting an inhibitor of a cysteine pathway enzyme, and combining said inhibitor, in an amount effective to reduce hair growth, with a non-toxic, dermatologically acceptable vehicle or carrier.

16. A method according to claim 15, wherein said vehicle or carrier is adapted to be spread upon the skin of a mammal.

17. A method according to claim 15, wherein a cosmetic composition is produced.

18. A method according to claim 15, wherein said inhibitor is as defined in any one of claims 2 to 8.

19. The new use of an inhibitor of a cysteine pathway enzyme for reducing hair growth.

20. A composition when used for inhibiting mammalian hair growth, which includes an inhibitor of a cysteine pathway enzyme in an amount effective to reduce hair growth, and a non-toxic, dermatologically acceptable vehicle or carrier.

21. A composition according to claim 20, wherein said inhibitor is as defined in any one of claims 2 to 8.

22. A composition according to claim 20, which is a cosmetic composition.

INTERNATIONAL SEARCH REPORT

Inter ›nal Application No
PCT/US 95/02902

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K7/06 A61K7/07

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,93 08687 (HANDELMAN,JOSEPH,H.) 13 May 1993 *Page7:claim 1* ---	1
A	WO,A,86 02269 (HANDELMAN,JOEEPH,H.) 24 April 1986 cited in the application *Page 14 :claim 1* & US,A,4 720 489 (SHANDER,DOUGLAS) ---	1
A	US,A,5 095 007 (GURPREET S. AHLUWALIA) 10 March 1992 cited in the application *Page 1: abstract* --- -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
28 July 1995	- 7. 08. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Luyten, H

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/US 95/02902

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,92 00069 (HANDELMAN, JOSEPH,H.) 9 January 1992 cited in the application *Page 7: claims* & US,A,5 096 911 (AHLUWALIA, GURPREET ET AL)	1
A	WO,A,92 03140 (HANDELMAN,JOSEPH H.) 5 March 1992 cited in the application *Page 8 ;claim1* & US,A,5 132 293 (SHANDER ET AL)	1
A	WO,A,92 11007 (HANDELMAN,JOSEPH,H.) 9 July 1992 cited in the application & US,A,5 143 925 (SHANDER ET AL)	1
A	WO,A,85 02543 (KASZYNSKI,EDWIN,G.) 20 June 1985 cited in the application *Page 12: claim 1* & US,A,4 885 289 (BREUER,MIKLOS,M.)	1
P,A	WO,A,94 27586 (HANDELMAN,JOSEPH,H.) 8 December 1994	1
P,A	WO,A,94 27563 (HANDELMAN,JOSEPH,H.) 8 December 1994 *Page 7: claim1*	1

1

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/US 95/02902

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9308687	13-05-93	AU-A-	3062792	07-06-93
		CA-A-	2122002	13-05-93
		EP-A-	0612211	31-08-94
		JP-T-	7504646	25-05-95
WO-A-8602269	24-04-86	US-A-	4720489	19-01-88
		AU-B-	590730	16-11-89
		AU-A-	4867385	02-05-86
		CA-A-	1262335	17-10-89
		DE-A-	3585526	09-04-92
		EP-A,B	0198893	29-10-86
		JP-B-	6053680	20-07-94
		JP-T-	62500932	16-04-87
		NO-B-	174832	11-04-94
US-A-4720489	19-01-88	AU-B-	590730	16-11-89
		AU-A-	4867385	02-05-86
		CA-A-	1262335	17-10-89
		DE-A-	3585526	09-04-92
		EP-A,B	0198893	29-10-86
		JP-B-	6053680	20-07-94
		JP-T-	62500932	16-04-87
		NO-B-	174832	11-04-94
		WO-A-	8602269	24-04-86
US-A-5095007	10-03-92	AU-A-	8928991	26-05-92
		CA-A-	2094491	25-04-92
		EP-A-	0554363	11-08-93
		JP-T-	6502648	24-03-94
		WO-A-	9207569	14-05-92
WO-A-9200069	09-01-92	US-A-	5096911	17-03-92
		AU-A-	8209491	23-01-92
		EP-A-	0607124	27-07-94
		JP-T-	6502389	17-03-94
US-A-5096911	17-03-92	AU-A-	8209491	23-01-92
		EP-A-	0607124	27-07-94
		JP-T-	6502389	17-03-94
		WO-A-	9200069	09-01-92

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/US 95/02902

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9203140	05-03-92	AU-B-	657710	23-03-95
		AU-A-	8723291	17-03-92
		CA-A-	2088909	15-02-92
		EP-A-	0543949	02-06-93
		JP-T-	6500335	13-01-94
		US-A-	5132293	21-07-92
US-A-5132293	21-07-92	AU-B-	657710	23-03-95
		AU-A-	8723291	17-03-92
		CA-A-	2088909	15-02-92
		EP-A-	0543949	02-06-93
		JP-T-	6500335	13-01-94
		WO-A-	9203140	05-03-92
WO-A-9211007	09-07-92	AU-B-	656550	09-02-95
		AU-A-	9165391	22-07-92
		EP-A-	0563301	06-10-93
		JP-T-	6504057	12-05-94
		US-A-	5143925	01-09-92
US-A-5143925	01-09-92	AU-B-	656550	09-02-95
		AU-A-	9165391	22-07-92
		EP-A-	0563301	06-10-93
		JP-T-	6504057	12-05-94
		WO-A-	9211007	09-07-92
WO-A-8502543	20-06-85	AU-B-	584070	18-05-89
		AU-A-	3745885	26-06-85
		CA-A-	1251737	28-03-89
		DE-A-	3486090	08-04-93
		EP-A,B	0165970	02-01-86
		JP-B-	7045382	17-05-95
		JP-T-	61500966	15-05-86
		US-A-	4885289	05-12-89
US-A-4885289	05-12-89	AU-B-	584070	18-05-89
		AU-A-	3745885	26-06-85
		CA-A-	1251737	28-03-89
		DE-A-	3486090	08-04-93
		EP-A,B	0165970	02-01-86

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/US 95/02902

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-4885289		JP-B- 7045382	17-05-95
		JP-T- 61500966	15-05-86
		WO-A- 8502543	20-06-85
WO-A-9427586	08-12-94	AU-B- 7018194	20-12-94
WO-A-9427563	08-12-94	AU-B- 6833194	20-12-94